Breast Cancer Surveillance Consortium Proposal Form

Project Title: The Effect of Breast Augmentation on Mammographic Screening and Cancer Severity

Short title (5 words or less): Augmentation paper

Project Leader:

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Purpose of data request (check all that apply):

- X data analysis for manuscript (target journal: __*JAMA*_____)
- ❑ preliminary data for grant proposal
- ❑ inputs for simulation model
- ❑ development of statistical methods
- ❑ other _____ (describe)

Type of data request:

- ❑ aggregate data
- ❑ de-identified individual level data without dates, zipcodes, or BCSC site identifiers
- ❑ de-identified individual level data with
  - ❑ dates
  - ❑ zipcodes
  - X masked BCSC site identifiers

Any data request that includes dates, zipcodes, or masked BCSC site identifiers will require completion of a HIPAA data use agreement following approval of proposal

- ❑ other _____ (describe)

Preference for person who will perform data analysis:

- X project leader or collaborator
- X analyst from Statistical Coordinating Center
- ❑ other _____(describe)

Proposed Timetable (include initiation and completion dates and any anticipated deadlines)**:**

Research Objective/Major Hypotheses:
Please include the following: Background, Objective, Methods (including mockup draft tables, inclusion/exclusion criteria for study subjects, study time period, power analyses, and analytic plan)

Background: Although many studies have shown that breast implants do not increase the risk of breast cancer (1), women with breast implants may be more likely to be diagnosed with more advanced disease than women without implants since breast augmentation interferes with routine mammographic evaluation (2-8). Previous studies on breast cancer following breast augmentation give contradictory results (1-3, 9-13); however, most of these studies were limited by very small sample sizes. In addition, all studies included cases that were diagnosed prior to 1989 when radiologists' began using implant displacement views, which improve visualization of breast tissue in women with implants (7).

Two larger studies on breast cancer following augmentation mammoplasty were recently published by Brinton and colleagues (1) and Skinner and colleagues (2). The Brinton *et al.* study concentrated on risk of breast cancer, but also compared stage of cancer in 116 augmented women to 52 non-augmented women who had undergone other types of plastic surgery. Although they found women with breast implants tended to have later stage disease (35% versus 17% with regional or distant disease), this difference was not statistically significant; however, the differences remained after adjusting for other factors such as access to medical care. The study conducted by Skinner and colleagues (2) compared 99 cancer cases in augmented women to 2,857 cases in non-augmented women. They found that mammography was less sensitive for augmented women (54% compared to 95%) and that augmented women were more likely to be diagnosed with palpable tumors (83% compared to 59%), invasive carcinoma (82% compared to 72%), and nodal involvement (48% compared to 36%).

Data from the Breast Cancer Surveillance Consortium offer a unique opportunity to more closely examine the effect of breast augmentation on mammographic sensitivity and cancer severity at diagnosis using more recent data from multiple sites throughout the United States. We expect to have more power to detect differences than the previous studies given the large number of cancers in non-augmented women available for comparison (however, we will likely have slightly fewer numbers of cancers in augmented women). In addition, we can adjust for hormone therapy (HT), family history of breast cancer, and time since last mammogram.

Research Question: Does the distribution of characteristics associated with cancer severity (e.g., stage, grade, tumor size) differ for women with breast augmentation mammoplasty compared to those without breast augmentation? Does the sensitivity of screening mammography vary among women with breast augmentation mammoplasty compared to those without breast augmentation?

Objective: To examine the effect of breast augmentation on accuracy of screening mammography and severity of cancer at diagnosis. We will compare sensitivity of screening mammography, mode of diagnosis (screening mammogram, diagnostic mammogram, or interval cancer), % of invasive cancer (compared to DCIS), tumor stage, tumor size, tumor grade, nodal status, and ER status for augmented and non-augmented women.

Population: Women with invasive cancer or DCIS diagnosed 1994 or later. Exclusion criteria include personal history of breast cancer (self-report or found in the registry), self-report of

mastectomy or breast reconstruction prior to diagnosis, self-report of breast augmentation to only one breast, or missing or inconsistent self-report of breast augmentation

Study Period: We will include all women with cancer diagnosed from January 1994 to present.

Methods: We will select all women diagnosed with their first invasive cancer or DCIS from January 1994 to present. For these women, we will look at their most recent exam prior to diagnosis (either diagnostic or screening) and their most recent screening exam within two years of diagnosis (which will be the same exam for women with screen-detected cancer). We may need to consider alternative definitions of a screening exam if *indication* is routinely coded as diagnostic for routine mammograms in asymptomatic women with implants. We will classify augmentation status using self-reported breast augmentation at the screening exam. Among women with only a diagnostic exam, we will use self-reported augmentation at the time of the diagnostic exam. We exclude women with self-report of breast augmentation to only one breast, women with insufficient information about self-report of breast augmentation, women with self-report of mastectomy or breast reconstruction, and women with prior self-report of breast augmentation (if she did not report breast augmentation at either exam).

To determine mode of detection, we will look at all mammograms that occurred within twelve months of diagnosis. Women without a mammogram will be classified as an interval cancer. We will need to agree on the best way to classify women with mammograms as screen or diagnostic detected (for example, how do we classify women with short-interval follow-up?).

We will estimate sensitivity separately for screening and diagnostic exams. We will look at the most recent exams within 24 months of diagnosis.

Data Source: BCSC pooled data.

Data Analysis: We will use logistic regression (and polytomous or linear regression where noted), adjusting for age, site, HT use, family history, and time since last mammogram (prior to the mammogram from which the cancer was detected) to compare the probability of the following outcomes in augmented women compared to non-augmented women:

1. Invasive disease versus DCIS
2. Mode of detection (screening, diagnostic, interval – polytomous regression)
3. Stage II or higher disease
4. Tumor 20 mm or greater (possible treat as continuous with linear regression)
5. Grade III or higher disease
6. Nodal involvement
7. ER negative status

In addition, to test for an effect of augmentation on mammographic sensitivity, we will fit logistic regression models, adjusting for age, site, HT use, family history, and time since last mammogram (prior to the mammogram from which the cancer was detected), to compare the probability of a positive screening mammogram and the probability of a positive diagnostic mammogram (separate models).

Power analysis: Brinton and colleagues (1) found that 35% of women with augmented breasts had stage II or higher disease (regional or distant disease) compared to 17% of women without augmentation. If we have 70 augmented women and 17,000 non-augmented women with cancer, we will have over 80% power to detect this difference.

Variables needed from the SCC:

Outcome variables
DCIS or invasive
Stage
Tumor size
Nodal involvement
Grade
ER status
Mode of detection (screening vs. diagnostic exam)

Covariates
Age at diagnosis
Site
Time since last screening mammogram (prior to dx)
Result of last screening mammogram (within two years prior to dx)
Indicator of mammogram within two years of the mammogram that lead to diagnosis
Indicator of mammogram within two years of the most recent screening mammogram prior to diagnosis
HT use
Family history of breast cancer
Self-report of symptoms
Race

Tables:

Table 1. Characteristics of study population.
Table 2. Mode of detection and sensitivity of screening and diagnostic exams by augmentation.
Table 3. Distribution of cancer characteristics by augmentation.
Table 4. Change in odds of outcome for women with augmentation compared to women without augmentation.

Table 1. Characteristics of study population.

	Breast Augmentation		No Augmentation	
	N	(%)	N	(%)
Age (years)				
30-39				
40-49				
50-59				
60-69				
70+				
Education				
High School or Less				
Some College				
College Graduate or beyond				
Missing				
Mammogram within 2 years prior to diagnosis?				
Yes				
No				
HT Status				
HT user				
Non-user				
Family history of BC				
Yes				
No				
Self-report of symptoms				
Lump or nipple discharge				
Other symptoms				
None				
Missing				
Race				
White				
Black				
Asian				
Native American/Alaskan Native				
Other (includes Mixed)				
Missing				

Table 2. Mode of detection and sensitivity of screening and diagnostic exams by augmentation.

	Breast Augmentation		No Augmentation	
	N	(%)	N	(%)
Mode of Detection				
Screening Exam				
Diagnostic Exam				
Interval Cancer				
Result of Prior Screening Exam				
TP				
FN				
Result of Prior Diagnostic Exam				
TP				
FN				
Sensitivity (95% CI)				
Screening exam				
Diagnostic exam				

Table 3. Distribution of tumor characteristics by augmentation.

	Breast Augmentation		No Augmentation	
	N	(%)	N	(%)
Invasive vs. DCIS				
Invasive				
DCIS				
Stage				
Stage 0				
Stage I				
Stage II				
Stage III or IV				
Tumor Size				
<10 mm				
11 - 19 mm				
20 + mm				
Grade				
Grade I				
Grade II				
Grade III				
Grade IV				
ER Status				
Positive				
Negative				
Nodal Involvement				
Yes				
No				

Table 4. Change in odds of outcome for women with augmentation compared to women without augmentation.

	Augmentation vs. No Augmentation	
Outcome	OR	(95% CI)
Positive screening exam		
Mode of detection:		
Diagnostic vs. Screen detected		
Interval vs. Screen detected		
Invasive cancer versus DCIS		
Stage >= 2		
Tumor Size > 20 mm		
Grade III or IV		
ER Negative		
Nodal involvement		

Reference List

(1) Brinton, L. A., Lubin, J. H., Burich, M. C., Colton, T., Brown, S. L., and Hoover, R. N. Breast cancer following augmentation mammoplasty (United States). Cancer Causes Control 11(9), 819-27. 2000.

(2) Skinner, K. A., Silberman, H., Dougherty, W., Gamagami, P., Waisman, J., Sposto, R., and Silverstein, M. J. Breast cancer after augmentation mammoplasty. Ann Surg Oncol 8(2), 138-44. 2001.

(3) Carlson, G. W., Curley, S. A., Martin, J. E., Fornage, B. D., and Ames, F. C. The detection of breast cancer after augmentation mammaplasty. Plast Reconstr Surg 91(5), 837-40. 93.

(4) Fajardo, L. L., Harvey, J. A., McAleese, K. A., Roberts, C. C., and Granstrom, P. Breast cancer diagnosis in women with subglandular silicone gel-filled augmentation implants. Radiology 194(3), 859-62. 95.

(5) Eklund, G. W., Busby, R. C., Miller, S. H., and Job, J. S. Improved imaging of the augmented breast. AJR Am J Roentgenol 151(3), 469-73. 88.

(6) Silverstein, M. J., Handel, N., Gamagami, P., Waisman, E., and Gierson, E. D. Mammographic measurements before and after augmentation mammaplasty. Plast Reconstr Surg 86(6), 1126-30. 90.

(7) Eklund, G. W. and Cardenosa, G. The art of mammographic positioning. Radiol Clin North Am 30(1), 21-53. 92.

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(9) Schirber, S., Thomas, W. O., Finley, J. M., Green, A. E., and Ferrara, J. J. Breast cancer after mammary augmentation. South Med J 86(3), 263-8. 93.

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(12) Clark, C. P., Peters, G. N., and O'Brien, K. M. Cancer in the augmented breast. Diagnosis and prognosis. Cancer 72(7), 2170-4. 93.

(13) Cahan, A. C., Ashikari, R., Pressman, P., Cody, H., Hoffman, S., and Sherman, J. E. Breast cancer after breast augmentation with silicone implants. Ann Surg Oncol 2(2), 121-5. 95.

To be completed by the Statistical Coordinating Center

Date Received by the SCC: April 23, 2001

Date of Steering Committee Review: April 24, 2001

Steering Committee Action:

X Approved ☐ Returned for Additional Information
☐ Disapproved

SCC Analyst: Diana Miglioretti

Date of Correspondence with Project Leader: April 24, 2001

IRB Approval Date (submitted by Project Leader): July 20, 1999

Anticipated Project Start Date: Winter 2002/2003